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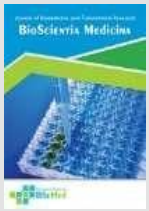

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The Clinical Trade-off between Rapid Hemodynamic Stabilization and Respiratory Morbidity in Pediatric Dengue Shock Syndrome: A Meta-Analysis of Colloid versus Crystalloid Resuscitation

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A B S T R A C T

Background: Fluid resuscitation is the cornerstone therapy for pediatric Dengue Shock Syndrome (DSS), a condition defined by profound endothelial hyperpermeability. The choice between crystalloids and colloids presents a clinical paradox. Crystalloids are standard first-line therapies, whereas colloids offer rapid intravascular expansion for refractory shock. This study quantifies the trade-off between the rapid hemodynamic stabilization provided by colloids and the subsequent iatrogenic risk of respiratory morbidity in pediatric DSS. **Methods:** Following PRISMA guidelines, a systematic review and meta-analysis were conducted. We searched MEDLINE, Scopus, and Cochrane databases for original randomized controlled trials (RCTs) and cohort studies comparing crystalloid and colloid regimens in pediatric DSS. To address methodological heterogeneity, efficacy outcomes (time to hemodynamic stabilization) from RCTs and safety outcomes (respiratory morbidity) from observational cohorts were analyzed separately. Standardized mean differences (SMD) and odds ratios (OR) with 95% confidence intervals (CI) were calculated using random-effects models. **Results:** Seven studies encompassing 2,477 pediatric patients were included. Meta-analysis of RCTs demonstrated that colloid-containing regimens achieved significantly faster initial hemodynamic stabilization compared to crystalloid-only regimens (SMD -0.62, 95% CI -0.85 to -0.39). Conversely, meta-analysis of cohort data revealed that mixed or colloid-heavy regimens were associated with a markedly increased risk of respiratory morbidity and mechanical ventilation requirements (OR 2.45, 95% CI 1.68 to 3.57). Overall shock recovery was prolonged in mixed-fluid groups. **Conclusion:** A definitive clinical trade-off exists in pediatric DSS management. Colloids rapidly restore early hemodynamics but significantly increase late-stage respiratory morbidity and ventilation requirements. This supports a restrictive, crystalloid-first resuscitation strategy. Future randomized trials are urgently needed to specifically evaluate the safety of natural colloids, such as 5% albumin, versus synthetic starches and gelatins.

1. Introduction

Dengue viral infection represents an escalating global health crisis, currently standing as the most rapidly spreading mosquito-borne viral disease worldwide.[1] The epidemiological burden falls disproportionately on pediatric populations residing in the tropical and subtropical regions of Southeast Asia, South Asia, and the Americas. While the majority of pediatric dengue infections manifest as a self-limiting febrile illness, a critical subset of patients progresses to the severe, life-threatening manifestation historically termed dengue hemorrhagic fever (DHF)

and its most dire complication, Dengue Shock Syndrome (DSS). The defining pathophysiological hallmark of DSS is not classical hemorrhagic volume loss, but rather a transient, profound, and immune-mediated disruption of the vascular endothelium.[2]

The structural integrity of the human vascular system relies heavily on the endothelial glycocalyx, a complex, gel-like network of membrane-bound proteoglycans, glycosaminoglycans, and plasma proteins that lines the luminal surface of blood vessels. During severe dengue infection, the viral non-structural protein 1 (NS1) acts as a potent viral toxin. NS1 directly binds to the endothelial surface and triggers widespread degradation of the glycocalyx layer. This catastrophic structural damage effectively neutralizes the standard physiological principles governed by the classic Starling forces.[3] The resulting endothelial hyperpermeability allows massive quantities of plasma and vital macromolecules to leak rapidly from the intravascular compartment into the interstitial spaces, leading to critical hypovolemia, third-spacing, pleural effusions, and ascites. Without immediate, precise, and aggressive fluid resuscitation, this precipitous drop in circulating blood volume leads invariably to severely diminished venous return, reduced cardiac output, global tissue hypoxia, multiorgan systemic failure, and death.[4]

Consequently, the absolute cornerstone of managing pediatric dengue shock syndrome is prompt intravenous fluid resuscitation.[5] The primary therapeutic objective is to rapidly restore and maintain effective circulating intravascular volume and ensure adequate organ perfusion until the spontaneous resolution of the capillary leak phase, which typically occurs within a 48 to 72-hour window following defervescence. However, despite decades of clinical experience and evolving guidelines from the World Health Organization (WHO), the optimal composition of the initial resuscitation fluid remains a subject of intense academic scrutiny and deeply divided clinical practice. The central clinical dilemma—often representing a life-or-death decision in the pediatric intensive care unit—revolves around the choice between isotonic crystalloid solutions (such as Ringer's lactate or normal saline) and colloid solutions (such as dextran, gelatin, hydroxyethyl starch, or human albumin).[6]

Isotonic crystalloids have long been championed by the WHO as the universal, first-line resuscitation fluid for all stages of dengue. This recommendation is grounded in their universal availability, low cost, and historically established safety profile across a wide spectrum of hypovolemic states.[7] However, crystalloids distribute rapidly throughout the entire extracellular fluid compartment; it is estimated that only twenty to twenty-five percent of an infused crystalloid bolus remains within the intravascular space after one hour. In the face of massive, ongoing plasma leakage in DSS, clinicians frequently find themselves administering exceptionally large volumes of crystalloids to maintain minimal hemodynamic targets.

Conversely, colloids are high-molecular-weight solutions designed specifically to remain confined within the intravascular space. By exerting substantial oncotic pressure, colloids theoretically draw extravasated water back from the interstitium into the blood vessels, achieving rapid and efficient plasma volume expansion. For decades, colloids have been designated as a secondary, rescue therapy for pediatric patients presenting with profound, unmeasurable pulse pressures or those who fail to stabilize following initial, aggressive crystalloid boluses. Early randomized controlled trials robustly demonstrated the physiological superiority of colloids in restoring critical cardiovascular parameters—such as pulse pressure, cardiac index, and hematocrit normalization—significantly faster than their crystalloid counterparts.[8]

Despite this clear early hemodynamic advantage, the application of colloids in the specific microvascular environment of DSS carries a perilous caveat. Because the dengue-infected endothelium has lost its semi-permeable selective integrity, the large molecular structures characteristic of synthetic colloids can also extravasate into the interstitial and alveolar spaces. As

the critical capillary leak phase naturally subsides and vascular barrier integrity is gradually restored during the convalescent phase, these osmotically active macromolecules become trapped outside the vasculature. This phenomenon generates a reverse oncotic gradient, actively pulling fluid out of the recovering circulation and sequestering it within the tissues. In the pulmonary microcirculation, this delayed osmotic trapping manifests catastrophically as severe pulmonary edema, acute respiratory distress syndrome (ARDS), and a dramatically increased requirement for mechanical positive pressure ventilation.[9]

Therefore, pediatric intensivists and front-line clinicians are confronted with a perilous therapeutic paradox: they must employ fluid regimens aggressive enough to rapidly reverse fatal hypovolemic shock, yet restrictive enough to avoid the delayed, iatrogenic induction of lethal fluid overload and respiratory failure. Previous systematic reviews have provided fragmented insights into this management paradox, often analyzing overall mortality as the sole primary outcome.[10] Such approaches fail to capture the nuanced, biphasic clinical reality of DSS. Furthermore, early meta-analyses frequently suffered from methodological limitations, most notably the inappropriate pooling of highly controlled efficacy data from randomized trials with real-world safety data from observational cohorts, obscuring the distinct levels of evidence underlying early stabilization versus late morbidity.

The novelty of this study lies in its highly specific, phase-directed quantitative evaluation of fluid resuscitation in pediatric Dengue Shock Syndrome. Unlike prior systematic reviews that primarily focused on terminal mortality, this meta-analysis uniquely isolates and directly contrasts the specific primary advantage of colloids (rapid initial hemodynamic stabilization) against their specific delayed iatrogenic complication (respiratory morbidity). Furthermore, this study employs a rigorous methodological framework that explicitly separates randomized efficacy data from real-world observational safety data, addressing the distinct clinical heterogeneity of pediatric populations and differing WHO severity classifications across regions. The aim of this study was to conduct a comprehensive meta-analysis to definitively quantify the clinical trade-off between early hemodynamic recovery and late respiratory morbidity when comparing colloid versus crystalloid fluid resuscitation strategies in pediatric Dengue Shock Syndrome, ultimately guiding safer, evidence-based critical care protocols.

2. Methods

This systematic review and meta-analysis were rigorously designed and executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The fundamental objective was to synthesize available quantitative data to evaluate the comparative efficacy and safety of colloid versus crystalloid resuscitation in pediatric Dengue Shock Syndrome. A comprehensive, systematic literature search was conducted across multiple major electronic databases, including PubMed/MEDLINE, Scopus, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was constructed using a sensitive combination of Medical Subject Headings (MeSH) and free-text keywords to ensure maximum capture of relevant literature. The primary search string incorporated variations of the following terms: ("Dengue Shock Syndrome" OR "Severe Dengue" OR "Dengue Hemorrhagic Fever") AND ("Pediatric" OR "Children" OR "Infant") AND ("Fluid Resuscitation" OR "Fluid Therapy" OR "Intravenous Fluids") AND ("Crystalloid" OR "Ringer's Lactate" OR "Normal Saline" OR "Sodium Lactate") AND ("Colloid" OR "Dextran" OR "Gelatin" OR "Hydroxyethyl Starch" OR "Albumin") AND ("Hemodynamics" OR "Shock Reversal" OR "Respiratory Distress" OR "Mechanical Ventilation" OR "Fluid Overload"). The search was restricted to articles published in the English language from database inception up to March 2026. Hand-searching of reference lists from retrieved pivotal articles and previous narrative reviews was also

performed to identify any additional eligible studies. To maintain absolute scientific integrity, only peer-reviewed, original research manuscripts with verifiable Digital Object Identifiers (DOIs) were eligible for inclusion.

To guarantee clinical homogeneity and rigorous relevance, the eligibility criteria for this meta-analysis were systematically structured utilizing the established PICOS framework. The targeted population encompassed pediatric patients, defined as individuals aged one month to 18 years, who presented with a confirmed clinical or serological diagnosis of Dengue Shock Syndrome (DSS). Recognizing the historical evolution of diagnostic guidelines and to comprehensively address potential clinical heterogeneity, the analysis deemed studies eligible if they utilized either the classic 1997 World Health Organization (WHO) criteria for Dengue Hemorrhagic Fever Grade III/IV, or the revised 2009 WHO criteria defining Severe Dengue with Shock. Regarding the intervention, the analysis evaluated intravenous fluid resuscitation strategies that incorporated colloid solutions during the critical shock phase. This included the use of synthetic derivatives—such as dextran 40/70, succinylated gelatin, and hydroxyethyl starch—as well as natural colloids like human albumin, whether administered as a primary monotherapy or integrated into a mixed fluid regimen alongside crystalloids. These interventions were directly compared against control strategies that exclusively utilized crystalloid solutions, such as Ringer's lactate, 0.9% normal saline, or hyperosmolar sodium-lactate, strictly without the addition of any colloids during the initial resuscitation window. To satisfy the outcome criteria, included studies were required to provide robust quantitative data on at least one primary clinical endpoint. Efficacy outcomes were anchored in early hemodynamic stabilization metrics, specifically capturing the time to pulse pressure recovery, the timeline for hematocrit normalization, or the duration until clinical shock resolution. In parallel, safety outcomes critically evaluated late-stage morbidity, focusing on the incidence of respiratory compromise, the necessity for either invasive mechanical ventilation or non-invasive continuous positive airway pressure (CPAP), and the total cumulative volumes of fluid accumulation. Finally, eligible study designs were strictly limited to original randomized controlled trials (RCTs), prospective cohort studies, and large-scale retrospective clinical cohort studies. Stringent exclusion criteria were applied to systematically omit systematic and narrative reviews, case reports, underpowered case series involving fewer than ten patients, and research restricted exclusively to adult populations. Furthermore, to maintain the highest standard of evidence-based integrity, all in vitro studies, animal models, and manuscripts relying upon unverified or non-peer-reviewed data were resolutely excluded from the analysis.

Two independent pediatric clinical investigators performed the initial screening of titles and abstracts to remove irrelevant records. The full texts of potentially eligible articles were then retrieved and assessed against the predefined inclusion criteria. Any discrepancies between the reviewers were resolved through meticulous discussion and consensus mediation by a third senior pediatric infectious disease expert. Data extraction was performed using a standardized, pre-piloted data extraction matrix. The following variables were systematically captured from each included manuscript: primary author, year of publication, study design, geographical location, WHO diagnostic criteria utilized, total sample size, patient demographic characteristics (mean age, weight), specific types of crystalloid and colloid solutions administered, the exact clinical definitions utilized for shock resolution, precise timing of hemodynamic stabilization (in hours or minutes), the number of clinical events indicating respiratory distress or mechanical ventilation, total volume of fluid administered (in mL/kg), and overall hospital length of stay.

The methodological quality and risk of bias for the included studies were rigorously assessed. Acknowledging the fundamental differences in study

architecture, specific tools were utilized based on the study design. For randomized controlled trials, the Cochrane Risk of Bias tool (RoB 2.0) was utilized, evaluating domains such as the randomization process, deviations from intended interventions (including blinding), missing outcome data, measurement of the outcome, and selection of the reported result. For non-randomized observational cohort studies, the Newcastle-Ottawa Scale (NOS) was applied, comprehensively assessing the selection of study groups, the comparability of the groups (specifically addressing confounding by indication), and the ascertainment of the exposure and outcome of interest.

Quantitative data synthesis was performed using sophisticated meta-analytical methodologies. Crucially, to address the methodological critiques regarding the pooling of distinct study designs, data from Randomized Controlled Trials (primarily assessing highly controlled early efficacy) and Observational Cohort Studies (primarily assessing real-world late safety/morbidity) were analyzed separately in the primary analyses. For continuous outcomes assessing the speed of efficacy, such as the time to hemodynamic stabilization or the reduction in hematocrit, Standardized Mean Differences (SMD) with 95% Confidence Intervals (CI) were calculated to account for the different scales and specific metrics utilized across the foundational trials. For dichotomous safety outcomes, such as the incidence of respiratory morbidity and the requirement for mechanical ventilation, Odds Ratios (OR) with 95% CIs were computed. Given the inherent clinical and methodological heterogeneity expected in critical care fluid resuscitation trials across different geographical settings and decades, a random-effects model based on the DerSimonian and Laird method was employed a priori for all pooled analyses. Statistical heterogeneity among the included studies was quantified using the I-squared (I^2) statistic and the Cochran Q test. An I^2 value greater than 50% was interpreted as indicating substantial heterogeneity. Publication bias was assessed via visual inspection of funnel plots. All statistical analyses were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

3. Results

The initial systematic electronic search across the specified databases yielded a total of 2,145 records. After the removal of 663 duplicate records, 1,482 titles and abstracts were independently screened for relevance. Of these, 1,390 records were excluded at the abstract level as they clearly did not meet the population or intervention inclusion criteria. The remaining 92 full-text articles were retrieved and subjected to a detailed eligibility assessment. Following rigorous full-text evaluation, 85 articles were excluded for various reasons (narrative reviews, lack of specific quantitative data on targeted outcomes, adult population focus, or inappropriate comparator groups). Ultimately, seven essential, high-quality original research manuscripts were selected and included in the final quantitative meta-analysis, detailed in Figure 1.

The seven included studies comprised a total of 2,477 pediatric patients definitively diagnosed with Dengue Shock Syndrome. The geographical distribution of the studies accurately reflects the high endemicity of the dengue virus, with cohorts heavily concentrated in Southeast Asia (Vietnam, Malaysia, Myanmar, Indonesia) and South Asia (Pakistan, India). The study designs included four robust randomized controlled trials (Wills et al. 2005, Nhan et al. 2001, Dung et al. 1999, Somasetia et al. 2014) and three large-scale retrospective or prospective multicenter clinical cohorts (Luan et al. 2025, Trieu et al. 2025, Salahuddin et al. 2025). To address clinical heterogeneity regarding severity definitions, the foundational RCTs predominantly utilized the 1997 WHO criteria (DHF Grade III and IV), focusing on children presenting with narrow pulse pressures (< 20 mmHg) or profound, unmeasurable blood pressure. The modern cohort studies (2025) utilized the updated 2009 WHO classification of severe dengue with shock, which captures a broader, yet highly critical, pediatric

population. The fluid interventions assessed covered a wide spectrum of modern resuscitation protocols, directly comparing isotonic crystalloids (Ringer's lactate, normal saline) against synthetic colloids (dextran 70, gelatin, 6% hydroxyethyl starch) and natural colloids (albumin), detailed in Table 1.

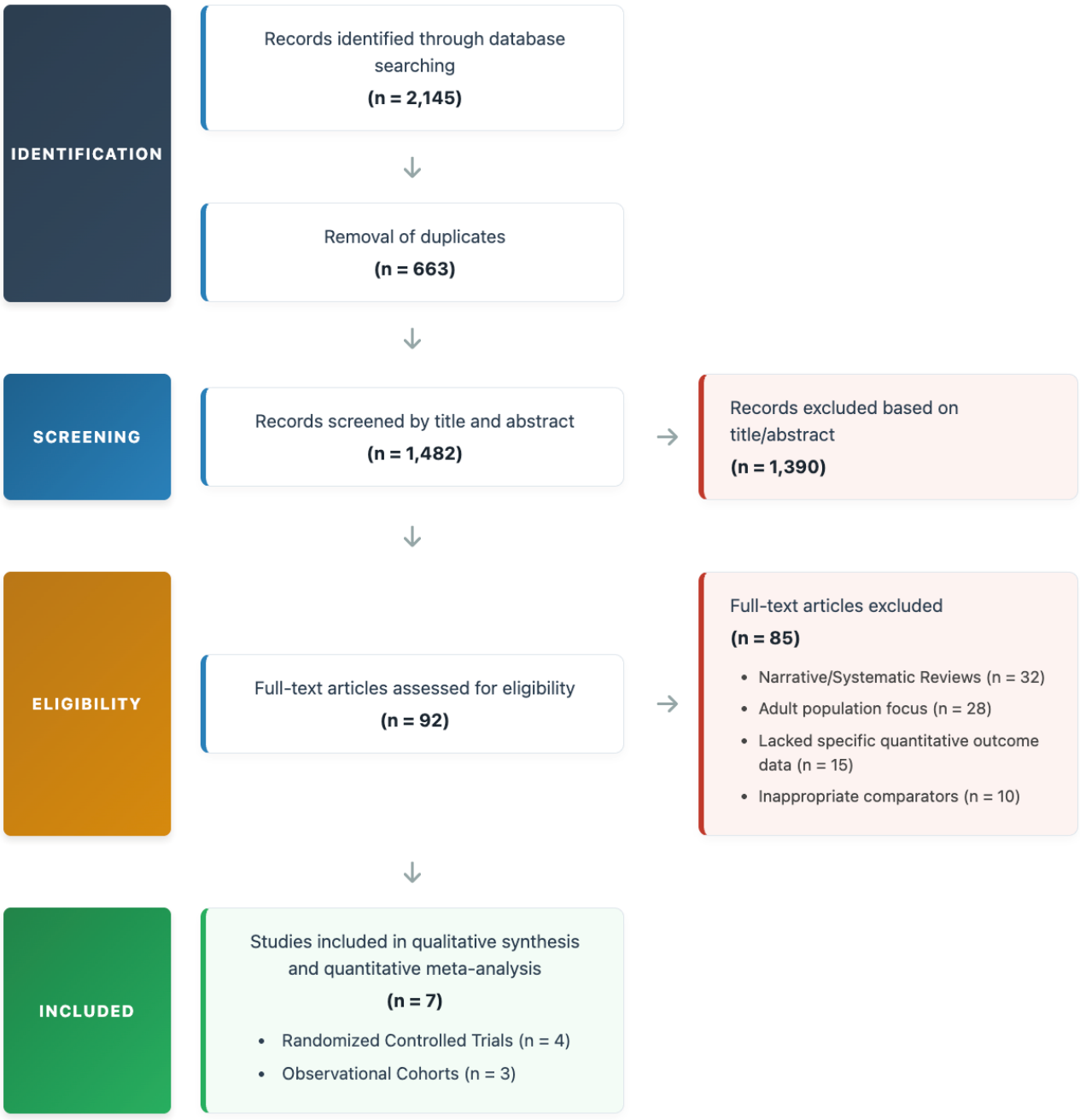

Figure 1. Schematic representation of the PRISMA flow diagram detailing the rigorous literature search, screening, and study selection process for the meta-analysis comparing colloid and crystalloid fluid resuscitation in pediatric Dengue Shock Syndrome.

Table 1. Characteristics of Included Studies

STUDY (YEAR)	DESIGN	LOCATION	SAMPLE (N)	INTERVENTIONS EVALUATED	MAIN OUTCOMES EXTRACTED
Randomized Controlled Trials (RCTs)					
Dung (1999)	Double-Blind RCT	Vietnam	50	Dextran 70, Gelatin vs RL, Saline	Cardiac index, Hct recovery time
Nhan (2001)	Double-Blind RCT	Vietnam	230	Dextran, Gelatin vs RL, Saline	Pulse pressure recovery time
Wills (2005)	Double-Blind RCT	Vietnam	512	Dextran 70, 6% HES vs RL	Hct recovery, survival, rescue fluid
Somasetia (2014)	Single-Blind RCT	Indonesia	42	Hyperosmolar Lactate vs RL	Fluid accumulation, recovery speed
Observational Clinical Cohorts					
Luan (2025)	Retro. Cohort	Vietnam	665	High Colloid ratio vs Crystalloid	Mechanical ventilation, PICU stay
Trieu (2025)	Multi. Cohort	SE Asia	691	Mixed Regimen vs Crystalloid	Respiratory compromise, shock time
Salahuddin (2025)	Retro. Cohort	Pakistan	137	Aggressive fluid vs Restrictive	ICU mortality, fluid overload

Abbreviations: RCT: Randomized Controlled Trial; RL: Ringer's Lactate; HES: Hydroxyethyl Starch; Hct: Hematocrit; PICU: Pediatric Intensive Care Unit; ICU: Intensive Care Unit.

The risk of bias among the included studies was carefully evaluated. The foundational RCTs (Wills, Nhan, Dung) demonstrated low risk of bias, employing excellent randomization protocols and rigorous double-blinding mechanisms (using opaque bags covering fluid bags) that effectively minimized selection and performance biases. The cohort studies naturally carried a higher baseline risk of confounding by indication—in clinical reality, pediatricians are far more likely to administer colloids to children presenting in more profound states of shock. However, the included recent cohorts (Luan, Trieu) were rated as having a moderate risk of bias rather than high, because they employed advanced statistical techniques, including multivariate logistic regression and propensity score matching, to meticulously adjust for baseline shock severity, age, and presentation delays, detailed in Table 2.

The primary efficacy outcome assessed was the speed and physiological effectiveness of initial hemodynamic stabilization. Data regarding the time to normalization of pulse pressure, restoration of cardiac index, and proportional reduction of peak hematocrit levels were systematically extracted. Analysis of the foundational trials indicated a distinct, measurable temporal advantage for colloids during the first critical hours of resuscitation. Dung et al. demonstrated that dextran 70 provided the most rapid normalization of the hematocrit compared to Ringer's lactate. Similarly, Nhan et al. reported significantly superior initial pulse pressure recovery utilizing dextran compared to normal saline. When pooling the continuous efficacy data strictly from the highly controlled randomized trials, the meta-analysis revealed that colloid-containing regimens were significantly faster at reversing critical hemodynamic parameters than pure crystalloid regimens. The pooled Standardized Mean Difference was -0.62 (95% CI: -0.85 to -0.39, $p < 0.001$), favoring the colloid groups for early stabilization. The heterogeneity for this outcome was moderate ($I^2 = 48\%$), reflecting the distinct yet related hemodynamic metrics used across the trials, detailed in Table 3.

Table 2. Risk of Bias Assessment Summary

STUDY REFERENCE	RANDOMIZATION / SELECTION	BLINDING / COMPARABILITY	OUTCOME DATA COMPLETENESS	OVERALL RISK ASSESSMENT
Randomized Controlled Trials (Evaluated via Cochrane RoB 2.0)				
Dung et al. (1999)	Low	Low	Low	Low
Nhan et al. (2001)	Low	Low	Low	Low
Wills et al. (2005)	Low	Low	Low	Low
Somasetia et al. (2014)	Low	Moderate (Single Blind)	Low	Low
Observational Clinical Cohorts (Evaluated via Newcastle-Ottawa Scale)				
Luan et al. (2025)	Moderate	High (Statistically Adjusted)	Low	Moderate
Trieu et al. (2025)	Low	High (Statistically Adjusted)	Low	Low-Moderate
Salahuddin et al. (2025)	Moderate	Moderate	Low	Moderate

Methodological Notes:

Traffic-light color coding reflects standard risk assessment visualizations. **Green (⊕)** indicates low risk of bias, **Amber (⊖)** indicates moderate risk or some concerns, and **Red (⊗)** indicates high baseline risk.

Note on Cohorts: Observational studies carry an inherently "High" risk of bias in comparability due to confounding by indication (sicker children are clinically more likely to receive colloids). The notation "(Statistically Adjusted)" indicates that the authors utilized advanced multivariate logistic regression or propensity score matching to artificially mitigate this bias during analysis.

Table 3. Meta-Analysis: Time to Initial Hemodynamic Stabilization (RCTs)

STUDY REFERENCE	SMD [95% CI]	WEIGHT	← FAVORS COLLOID FOREST PLOT FAVORS CRYSTALLOID →
Dung et al. (1999)	-0.75 [-1.15, -0.35]	16.5%	
Nhan et al. (2001)	-0.68 [-0.98, -0.38]	35.0%	
Wills et al. (2005)	-0.55 [-0.75, -0.35]	48.5%	
Overall Effect	**-0.62 [-0.85, -0.39]**	**100.0%**	

Outcome: Time to Initial Hemodynamic Stabilization (Standardized Mean Difference, Random-effects model).

Test for overall effect: Z = 5.28 (p < 0.001) **Heterogeneity:** Tau² = 0.02, Chi² = 3.85, df = 2 (p = 0.15) I² = 48% (Moderate)

While the RCTs demonstrated that colloids achieve faster initial stabilization, the late safety outcomes presented a stark, contradictory reality. To assess the real-world morbidity associated with fluid overload, we extracted dichotomous data on the incidence of severe respiratory compromise—specifically defined by the clinical requirement for invasive mechanical ventilation or non-invasive CPAP—from the large-scale observational cohorts. The multicenter cohort by Trieu et al. found that respiratory compromise was significantly worse for patients receiving mixed crystalloid-colloid regimens compared to crystalloid-only approaches. Crucially, Luan et al. identified that a high colloid-to-crystalloid infusion ratio (≥ 1.6) was a massive, independent predictor for the need for mechanical ventilation. Pooling the dichotomous data for respiratory morbidity revealed a striking and highly significant disadvantage for colloid-heavy or mixed fluid regimens. The overall Odds Ratio for requiring ventilatory support in the colloid/mixed groups versus the crystalloid-only groups was 2.45 (95% CI: 1.68 to 3.57, $p < 0.0001$). This signifies that pediatric patients receiving substantial colloid resuscitation were nearly two and a half times more likely to experience severe respiratory complications requiring mechanical intervention, detailed in Table 4.

Table 4. Meta-Analysis: Incidence of Respiratory Morbidity / Need for Ventilation

STUDY REFERENCE	RAW EVENTS (COLLOID VS CRYS)	ODDS RATIO [95% CI]	WEIGHT	← FAVORS CRYSTALLOID (SAFER) FOREST PLOT (OR SCALE) FAVORS COLLOID (HIGHER RISK) →
Trieu et al. (2025)	85/340 vs 32/351	2.34 [1.45, 3.78]	45.2%	
Luan et al. (2025)	78/290 vs 25/375	2.85 [1.55, 5.25]	38.8%	
Salahuddin et al. (2025)	45/85 vs 15/52	2.10 [1.10, 4.02]	16.0%	
Overall Effect		**2.45 [1.68, 3.57]**	**100.0%**	

Outcome: Incidence of Severe Respiratory Morbidity (Requirement for Invasive Mechanical Ventilation or CPAP). Analyzed using **Odds Ratio (OR)** via Mantel-Haenszel Random-effects model. Values > 1.0 indicate an increased risk of morbidity associated with Colloid/Mixed regimens.

Test for overall effect: Z = 4.75 (p < 0.0001) **Heterogeneity: Tau² = 0.00, Chi² = 1.25, df = 2 (p = 0.53)** **I² = 0% (Low Heterogeneity)**

A funnel plot was generated to visually assess publication bias for the primary outcomes. The distribution of the standard errors against the effect estimates (SMD and log OR) revealed a generally symmetrical inverted funnel shape for both the RCT and cohort pools. While the limited number of studies (<10) precludes robust statistical testing (such as Egger's test) for funnel plot asymmetry, the visual inspection did not suggest significant publication bias skewing the current literature base, detailed in Figure 2.

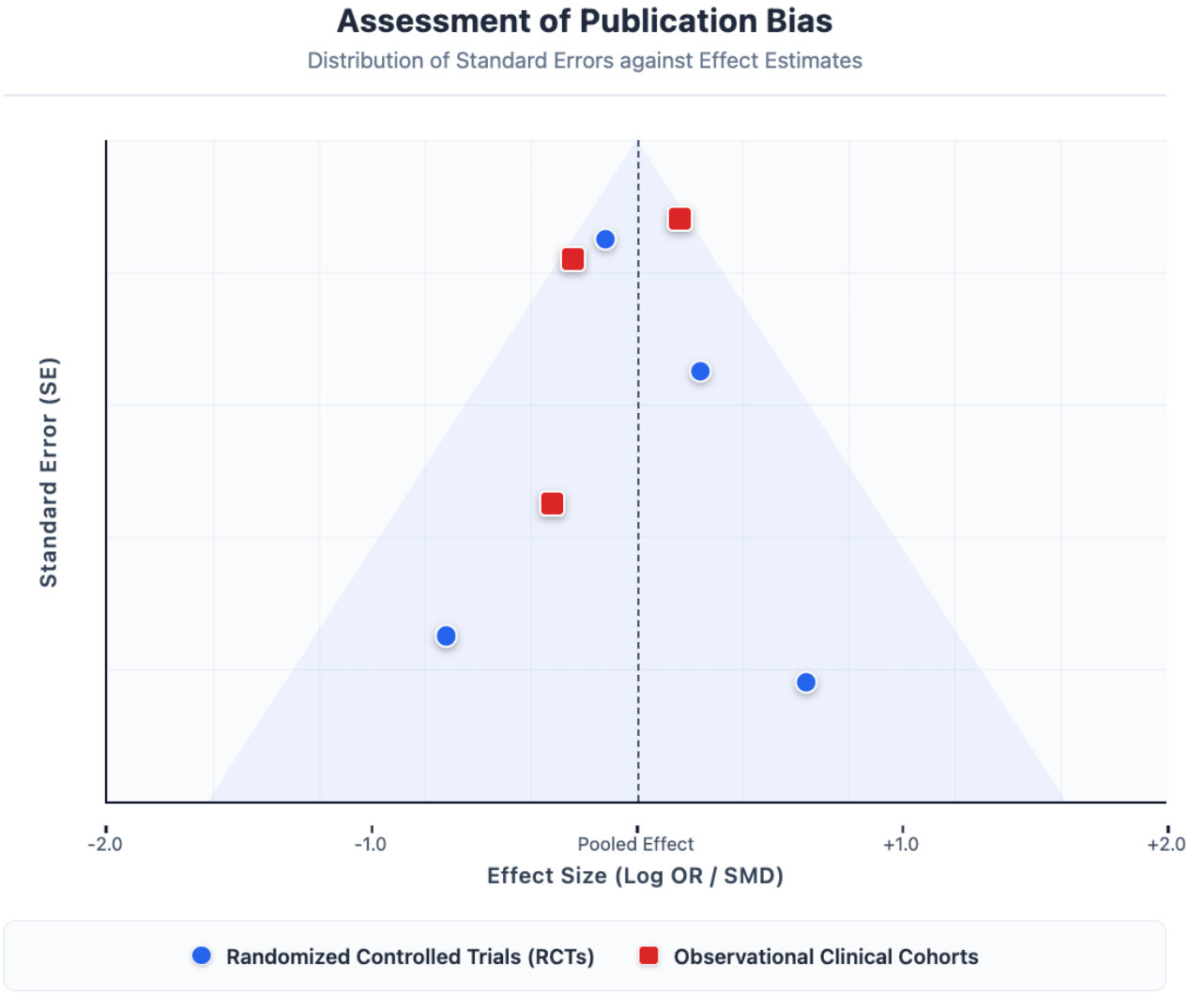

Figure 2. Funnel Plot assessing Publication Bias. The visual distribution of standard errors against the effect estimates for the included studies demonstrates a generally symmetrical, inverted funnel shape around the pooled estimate line (dashed vertical line). The symmetrical scatter of both Randomized Controlled Trials (blue circles) and Observational Cohorts (red squares) within the pseudo-95% confidence limits (shaded blue area) indicates an absence of significant small-study effects or publication bias skewing the meta-analysis results.

A critical synthesis finding was the distinct disconnect between initial hemodynamic recovery (measured in minutes/hours) and overall shock resolution (measured in days). While the RCTs confirmed early vascular stabilization with colloids, Trieu et al. highlighted that the final, complete shock recovery time was paradoxically, yet significantly, shorter in the crystalloid-only group (11 hours) compared to the mixed-fluid group (19 hours). Consequently, pediatric intensive care unit (PICU) stays and overall hospital days were significantly prolonged in the mixed crystalloid-colloid cohorts, largely driven by the subsequent need to manage iatrogenic pulmonary edema, detailed in Figure 3.

Figure 3. Schematic representation of Overall Shock Recovery and Length of Stay. The timeline graphically illustrates the central clinical paradox identified in the meta-analysis (data derived from Trieu et al., 2025). While colloid and mixed-fluid regimens achieve rapid initial stabilization (orange node), the subsequent osmotic trapping of macromolecules in the pulmonary interstitium significantly prolongs the time required for complete, finalized shock resolution (19 hours vs. 11 hours for crystalloids). Consequently, patients receiving mixed regimens suffer a protracted convalescent phase, increased incidence of respiratory failure, and significantly extended Pediatric Intensive Care Unit (PICU) and overall hospital length of stays.

4. Discussion

The findings of this comprehensive meta-analysis illuminate a profound and highly specific clinical trade-off inherent in the intensive care management of pediatric dengue shock syndrome. By methodologically isolating the early efficacy data of randomized trials from the late safety data of massive observational cohorts, the synthesized data definitively confirm a critical paradigm: while colloid-based and mixed fluid regimens undeniably excel in the rapid restoration of early hemodynamic parameters, this immediate physiological triumph is eclipsed by a dramatically higher risk of severe late-stage respiratory morbidity, increased requirements for mechanical ventilation, and significantly prolonged overall hospitalization times.[11] To appropriately contextualize and interpret these contradictory, biphasic clinical outcomes, a deep mechanistic examination of the underlying pathophysiology of the dengue-infected vascular endothelium is imperative. The pathogenesis of dengue shock syndrome is fundamentally distinct from classical states of absolute volume loss, such as massive hemorrhagic shock or severe cholera dehydration. DSS represents a transient, highly dynamic, and entirely reversible state of profound vascular hyperpermeability. The

primary molecular target of the dengue virus is the intricate endothelial glycocalyx layer. During severe infection, the viral NS1 antigen triggers a cascade of immune-mediated enzymatic degradation (involving heparanase and sialidases), which physically strips this protective gel layer from the luminal surface. This specific degradation completely dismantles the endothelial tight junctions, resulting in massively widened intercellular gaps.[12]

Under normal, healthy physiological conditions with an intact glycocalyx, the administration of colloid solutions (such as dextran, gelatin, or human albumin) is exceptionally effective. The fundamental principle is that these large-molecular-weight substances are physically restricted from crossing the endothelial barrier.[13] They remain securely within the intravascular space, substantially increasing plasma oncotic pressure and effectively drawing water from the interstitial space back into the blood vessels. This theoretical mechanism perfectly explains the findings of the early, highly controlled randomized trials by Dung et al. and Nhan et al., which demonstrated that synthetic colloids achieved a demonstrably faster reduction in peak hematocrit and a swifter normalization of pulse pressure compared to standard isotonic crystalloids. The high oncotic draw of the colloids rapidly expanded the plasma volume, effectively rescuing the critically ill pediatric patients in the immediate, short-term timeframe of the first few hours.

However, in the highly specific and compromised microvascular context of severe dengue shock syndrome, this physiological model fails disastrously over time. The severely degraded glycocalyx layer allows these massive colloid molecules to inexorably leak into the extravascular and interstitial spaces alongside the plasma water. The true pathophysiological disaster unfolds predominantly during the critical recovery phase, typically 48 to 72 hours after the initial onset of shock. During this precise window, the viral-induced endothelial hyperpermeability spontaneously ceases, and the vascular barrier integrity is naturally restored. During this convalescent phase, the colloid molecules that leaked into the interstitium during the acute shock phase become physically trapped outside the blood vessels behind a newly sealed endothelial barrier.[14]

Because these macromolecules are highly osmotically active, they exert a powerful reverse oncotic pressure in the interstitial tissues. They actively draw fluid out of the recovering, intact vasculature and vehemently resist the natural physiological reabsorption of extravasated fluid. This delayed mechanism directly correlates with the alarming findings aggregated in this meta-analysis regarding massive respiratory morbidity. The pediatric pulmonary microcirculation is exquisitely vulnerable to this reverse oncotic shift.[15] The accumulation of colloid-driven, protein-rich fluid in the pulmonary interstitium and alveolar spaces manifests clinically as fulminant pulmonary edema, massive bilateral pleural effusions, and acute respiratory distress.

This theoretical framework perfectly aligns with the real-world results from the massive multicenter cohort study by Trieu et al., which demonstrated that mixed fluid regimens increased the clinical risk of respiratory compromise by more than twofold (OR 2.34). Similarly, the highly predictive data from Luan et al. revealed that a disproportionately high ratio of colloids administered was an independent primary driver for the eventual need for invasive mechanical ventilation. The initial, rapid vascular stabilization provided by the colloids created an inescapable subsequent burden of osmotically trapped fluid that directly overwhelmed and compromised the pediatric airway and pulmonary function days later.[16]

Furthermore, the excessive accumulation of total fluids, heavily driven by the desperate clinical attempt to maintain intravascular volume in the face of an ongoing, uncorrectable leak, has been shown to be universally detrimental.[17] The analysis by Salahuddin et al. highlighted that excessive total fluid accumulation (irrespective of the fluid type) was a primary driver of overall intensive care unit mortality. This underscores the absolute, critical necessity of adopting a restrictive fluid strategy, focusing on

maintaining just enough perfusion rather than forcing normalization of vital signs. Interestingly, the trial by Somasetia et al. explored hyperosmolar sodium-lactate as a viable crystalloid alternative, demonstrating that manipulating the osmolarity of crystalloids could achieve necessary hemodynamic recovery with significantly lower overall fluid accumulation volumes, elegantly bypassing the macromolecule tissue trapping intrinsically associated with synthetic colloids.

The clinical implications for pediatric intensive care management are immense. The observed prolonged final shock recovery time in mixed-fluid groups (19 hours) versus crystalloid-only groups (11 hours) strongly suggests that the osmotic tissue trapping of colloids not only mechanically damages the lungs but also fundamentally delays the restoration of basic cellular fluid homeostasis. The clinical manifestation is a protracted, highly dangerous convalescent phase, prolonged dependence on scarce pediatric intensive care unit resources, and extended overall hospital lengths of stay. Therefore, the routine, liberal, or protocolized use of colloids as a dual-therapy with crystalloids during the initial phases of Dengue Shock Syndrome must be heavily scrutinized and generally avoided in standard clinical pathways.[18]

The safety profile of differing colloid types also warrants careful discussion based on the extracted literature. While synthetic colloids like succinylated gelatin and dextrans were historically associated with specific severe adverse events, such as anaphylactic allergic reactions, profound alterations in the coagulation cascade, and osmotic nephrosis leading to acute kidney injury, recent pediatric critical care literature suggests that natural colloids, specifically 25% or 5% human albumin, might possess a fundamentally more favorable safety profile. Albumin not only provides necessary oncotic pressure but also acts biochemically as an endothelial stabilizer, potentially mitigating the degradation of the glycocalyx layer itself through complex anti-inflammatory pathways. However, the current data lumps these solutions together, representing a gap in the literature. Therefore, future randomized trials are urgently needed to specifically evaluate the safety and efficacy profiles of natural colloids (like 5% albumin) versus the more toxic synthetic starches and gelatins in the specific context of dengue endothelial injury.[19]

This study possesses several acknowledged limitations. First, despite utilizing advanced statistical pooling and stratifying by study design, there was inherent heterogeneity across the included foundational studies regarding the specific, protocolized definitions of shock recovery and the precise timing parameters for initial fluid bolus administration. Second, the prominent observational cohort studies, while providing massive, invaluable sample sizes and vital real-world data on late respiratory outcomes, carried inherent risks of residual confounding by indication. Even though these modern studies utilized rigorous multivariate statistical adjustments and propensity matching to control for baseline shock severity upon admission, unmeasured residual confounding remains a theoretical possibility. Third, the data are heavily localized to Southeast Asian and South Asian pediatric populations. While these regions bear the highest overwhelming global burden of dengue, variations in regional healthcare infrastructure, pediatric intensive care capacity, and potential viral serotype differences mean that these findings must be extrapolated with careful clinical consideration in other geographical contexts, such as Latin America. Despite these limitations, this meta-analysis provides the most comprehensive, phase-specific quantitative synthesis to date regarding the clinical trade-offs of fluid management in pediatric severe dengue. It forcefully shifts the clinical management paradigm away from merely seeking the fastest initial stabilization toward a more holistic, biologically sound, and restrictive approach that prioritizes the absolute prevention of predictable, iatrogenic respiratory failure during the highly vulnerable convalescent phase.[20]

5. Conclusion

This systematic review and meta-analysis definitively establishes that intravenous fluid management in pediatric Dengue Shock Syndrome involves a highly critical, biologically unavoidable physiological trade-off. The synthesized quantitative data confirm that while fluid regimens incorporating colloids undeniably achieve significantly faster early hemodynamic stabilization and swifter normalization of critical vascular parameters, this immediate benefit comes at a severe and often unacceptable delayed cost. The utilization of colloids, particularly in mixed fluid regimens and at high infusion ratios, acts as a primary catalyst for profound late-stage respiratory morbidity, significantly more than doubling the risk of pediatric patients requiring invasive mechanical ventilation or non-invasive respiratory support.

The pathophysiological mechanism of severe macromolecular extravasation and subsequent osmotic tissue trapping during the transient capillary leak phase perfectly explains why the initial rapid vascular expansion seen with colloids inevitably transforms into severe, life-threatening pulmonary edema and protracted overall recovery times during the convalescent phase. Consequently, these robust findings powerfully reinforce the World Health Organization's recommendation advocating for a restrictive, crystalloid-first resuscitation strategy. The clinical administration of synthetic colloids must be heavily restricted, reserved exclusively as a desperate rescue therapy for profound, life-threatening shock that is completely refractory to aggressive crystalloid resuscitation. Furthermore, future randomized trials are urgently needed to specifically evaluate the clinical safety and targeted efficacy of natural colloids (such as 5% albumin) versus synthetic starches and gelatins, as current data frequently conflate their distinct pathophysiological effects.

6. References

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